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article

Symptomatic HIV seroconverting illness is associated with more rapid neurological impairment

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Objectives: To establish whether symptomatic seroconverting illness in HIV infected people is associated with more rapid development of neurological impairment.**Methods:** 166 HIV infected subjects with a known date of HIV infection enrolled in a longitudinal study of neurocognitive function were stratified by whether or not they had experienced a symptomatic seroconverting illness.**Results:** 29 of 166 (17.5%) dated HIV seroconverters had a history of symptomatic seroconverting illness. Though baseline neurocognitive function was similar, subjects with a symptomatic seroconverting illness developed clinical neurocognitive impairment significantly more rapidly than their asymptomatic counterparts in a survival analysis model (636 *v* 1075 days till impaired).**Conclusion:** Symptomatic seroconverting illness predisposes to more rapid neurocognitive impairment.

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Keywords: HIV; seroconverting illness; neurocognitive impairment

Introduction

Symptomatic acute retroviral infection occurs in 10–90%^{1–5} of patients with primary HIV infection. This illness is often ascribed to a “viral infection” and not recognised as a possible HIV seroconverting illness.^{6–8} Multiple studies have reported that a symptomatic initial infection is associated with a more rapidly progressive HIV disease.^{3 5 8–13}

Neurobehavioural complications occur commonly in HIV, and range from asymptomatic mild neurocognitive disturbances such as difficulties in attention and memory to frank dementia.¹⁴ Because HIV can be detected in cerebrospinal fluid (CSF) early in the course of infection, and since seroconverting illness is accompanied by neurological symptoms, we speculated that symptomatic HIV seroconverting illness might also be associated with a greater likelihood of developing neurocognitive impairment. To explore this issue we examined the hazard of becoming neurocognitively impaired as a function of experiencing seroconverting illness in a group of men for whom approximate dates of seroconversion were available.

Methods**PATIENTS**

The HIV Neurobehavioral Research Center (HNRC), a collaboration of the University of California at San Diego, the San Diego Veterans Affairs Medical Center, and the Naval Medical of San Diego, has evaluated the neurobehavioural effects of HIV infection in a cohort of HIV infected subjects since 1989. A detailed description of the cohort has been published previously.¹⁵ The relevant research committees at the three hospitals approved the research effort, and all subjects provided

written informed consent. We selected a subset of 166 HIV infected US military personnel who were enrolled in HNRC programme; these 166 subjects represent the dated military seroconverters with 2–6 years of complete follow up. We defined a dated seroconverter as a subject with a documented negative HIV ELISA within 3 years of their first positive HIV ELISA/western blot. The military health records of the dated seroconverters were then reviewed in detail for unexplained febrile illnesses during the period of documented HIV seroconversion. We defined a symptomatic seroconverting illness as an otherwise unexplained febrile episode lasting at least 3 days with one or more of the following symptoms—pharyngitis, adenopathy, diffuse rash, myalgias, headache, oral lesions, or malaise. There were 164 men and two women in the group, and their mean age was 28 years. The mean educational level was 12.9 years.

MEDICAL AND NEUROCOGNITIVE (NC) ASSESSMENT

Participants had had a comprehensive medical neuropsychological, psychiatric, and neurological examinations at study entry and at least annually thereafter. The annual NC evaluation consisted of an extended Halsted-Reitan battery with extra tests of attention, learning, memory, and language skills and the Wechsler Adult Intelligence Scale-Revised.¹⁵ Before analysis, all raw test scores were converted to age, education, and sex corrected standardised scores using published procedures based on data from large normative subject samples.^{15–17} Using these demographically adjusted scores, clinical ratings of NC functioning in eight major ability areas (verbal, abstraction, psychomotor, attention/speed of information processing, learning, memory, motor, and sensory)

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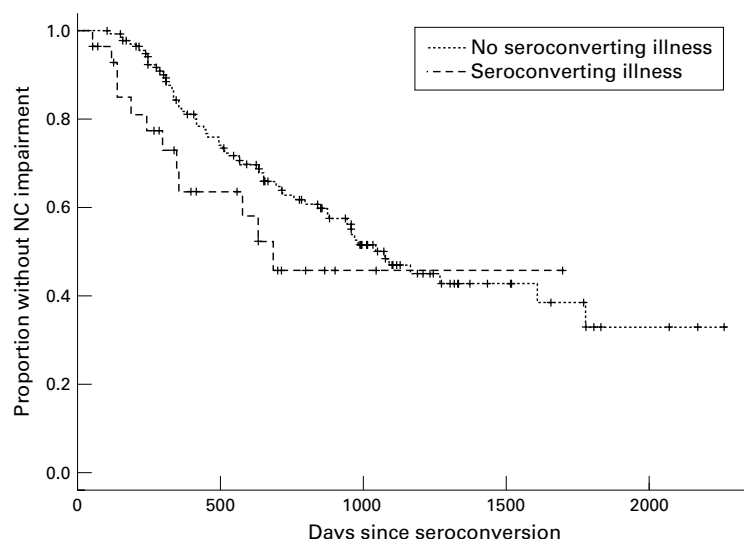


Figure 1 Survival plot.

and global functioning were made by an experienced neuropsychologist (RKH) who was blinded to the patient's HIV serostatus and history of symptomatic seroconverting illness. Clinical NC ratings were made on a scale of 1 to 9, with 1 representing above average performance, 9 reflecting severe impairment, and 5 or higher indicative of definite clinical impairment. The NC analysis was repeated at 6–12 month intervals. Medical evaluation included a CD4+ T lymphocyte count, directed physical and neurological examination, and storage (at -70°C) of aliquots of serum.

Results

Twenty nine of 166 dated seroconverters (17.5%) had a history of an otherwise unexplained febrile illness during the documented period of HIV seroconversion. All (by definition) had fever. Other symptoms and signs included pharyngitis in 20/29 (69%), malaise in 20/29 (69%), adenopathy in 17/29 (59%), myalgias in 12/29 (41%), headache in 12/29 (41%), oral lesions in 3/29 (10%), and rash in 3/29 (10%). The duration of the presumed seroconverting illness ranged from 3–180 days (mean 37, median 31 days). One of 29 had symptoms for less than 1 week, and only two were ill for more than 5 months. Only one of the 29 subjects had neurological symptoms or signs during the seroconverting illness; this patient received a lumbar puncture for meningeal symptoms and was found to have an aseptic meningitis which resolved without specific diagnosis or therapy.

The symptomatic seroconverters ($n=29$) did not differ from the asymptomatic cohort by age, race, educational level, or time since documented seroconversion to first blood draw, but they did have lower initial median CD4 cell counts (455 v 562 cells $\times 10^6/\text{l}$, t test, $p=0.03$). The median time to first CD4 count under 400 was reduced in the symptomatic group (577 v 960 days, Wilcoxon rank sum test, $p=0.02$).

Though initial global neurocognitive scores were similar in the symptomatic and asymptomatic groups (3.90 v 3.67 , t test, $p=0.4$),

patients with a symptomatic seroconverting illness developed clinical neurocognitive impairment more rapidly than their asymptomatic counterparts in a survival analysis model (636 v 1075 days till global functioning within the impaired range, $p=0.04$) (fig 1). Antiretroviral drug use was more common in the symptomatic seroconverting illness group, but this difference was not significant (66% v 47%, $p=0.1$).

Discussion

The seroconverting illnesses observed in our patients did not differ substantially from those in earlier reports.^{2,3} Most of the 29 patients who were seen by healthcare professionals during their seroconverting illness were felt to have suffered a "prolonged viral infection," but in no case was the correct viral infection (acute HIV) diagnosed. This is not surprising given the low HIV seroconversion rates (0.02%/year) among US military personnel and the much more common entities which resemble symptomatic primary HIV infection (Epstein-Barr virus, cytomegalovirus, toxoplasmosis, rubella, influenza, adenovirus, etc). Even studies designed specifically for early detection of seroconverting HIV disease have often missed typical cases.⁶

The frequency of symptomatic primary HIV disease in our cohort (17.5%) was similar to that observed in studies by Dorrucchi *et al*³ (10%), Veugelers *et al*,⁴ (13.8%) and Sinicco *et al*⁵ (17%), but much less than the 50–90% rates found by other investigators.^{1,2,9} What might account for these widely disparate rates of acute retroviral syndrome is unclear, but may be related to the threshold used to define a significant illness. We interviewed all newly documented HIV-1 seroconverters and reviewed their military health records to see if they had visited military healthcare providers with unexplained, prolonged febrile illnesses matching the usual description of the acute HIV seroconverting illness. It is probable that our methods overlooked less severe or atypical cases.

Our data support previous reports that have shown that symptomatic seroconversion is a major risk factor for more rapid CD4 depletion and/or AIDS.^{3–5,8–13} The poorer prognosis of patients with severe seroconverting illness is probably related to higher initial HIV loads and resultant rapid CD4 depletion¹⁸; whether such a relation will continue with the advent of highly active antiretroviral therapy (HAART) is unclear.

The new finding of our study is that symptomatic HIV seroconverting illness appears to predispose to more rapid neurocognitive deterioration. One study has found that neurological signs and symptoms occurring as part of an HIV seroconverting illness predispose to more rapid immunological deterioration,¹⁹ but this is distinct from our observation as only one of our 29 subjects had any neurological findings at the time of seroconverting illness.

HIV therapy using zidovudine appears to diminish the likelihood of severe neurocognitive sequelae²⁰; whether the use of HAART will

additionally benefit HIV infected people at risk remains unknown. The role of antiretroviral therapy in acute HIV infection is also unclear, but data from two placebo controlled trials suggest that zidovudine therapy during primary HIV infection improves the clinical course and CD4 counts.^{21 22} Whether treatment of symptomatic, primary HIV infection could modify the predisposition towards neurocognitive deficits is unknown, but given our increasing knowledge of the dynamics of early HIV infection, such intervention appears increasingly reasonable. Primary HIV infection may soon properly be regarded as a medical emergency,²³ carrying with it the risk of more rapid immunological and neurological impairment, but also perhaps providing an opportunity to initiate aggressive therapy and modify the course of illness.

The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.

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